Aβ fibrils essentially instantaneously, much faster than the fibril formation in wild-type (WT) Aβ1-40. To better understand the fibril-forming mechanism of the Japanese mutant peptide we have ran several long (μs) all atom explicit water molecular dynamics simulations of the mutant and WT peptide starting from the random-coil structure at two different temperatures (310 and 350 K). Our simulations showed that the ΔE22-Aβ1-39 mutant formed a stable semi-helical hairpin structure about 5 times faster than the WT. The helical hairpin conformation was less evident in WT trajectory and was quickly unfolded (particularly at 310K). The RMSF plots showed similar patterns of fluctuations in both the WT and mutant backbone atoms. However, the deletion of the E22 lowered the fluctuations of the mutant structure by about 2A at 310K. This fast and stable conformational change in ΔE22-Aβ1-39 can be used as a seed for the rapid fibril formation as observed in the experimental studies.

2047-Pos Board B66

Meld: Modeling Peptide-Protein Interactions

Alberto Perez, Justin MacCallum, Ken A. Dill.
Stony Brook university, Stony Brook, NY, USA.

We have recently developed Meld, a framework to Model with limited data. This framework combines sparse information coming from different experimental, bioinformatics and even evolution sources into a physics based methodology. The physics are implemented through an atomistic force field. An improved version of a hybrid Hamiltonian/temperature replica exchange [1] procedure allows us to handle the limited data along with the physics in a fashion that obeys detail balance. After our initial use in the CASP experiment (critical assessment of structure prediction) to predict the structures of proteins, we are now interested in showing how this procedure can help us to correctly model cases in which small peptides are interacting with proteins. This procedure has the advantage of having both peptide and protein as flexible units. Input data is introduced in the calculation as restraints. A naïve approach in which all the restraints are imposed at the same time would be a failure. Therefore, we allow for errors in the data by enforcing only a fraction of those restraints. We allow the physics to decide which restraints are the most compatible with the system. In this way, the conformational space is greatly reduced, and in combination with 100x improvements in sampling efficiency coming from GPU, allows us to converge into possible solutions. After our calculation is done, clustering methods allow us to identify the candidate docking regions. We plan to combine the top clustering solutions with all atom free energy methods based on confinement techniques [2] to identify the most likely binding site.

1. Sugita, Y., A. Kitao, and Y. Okamoto, ''Multidimensional replica-exchange method for free-energy calculations''. *Journal of Chemical Physics*, 113(15): p. 6042-6051 (2000).
2. Tyka, M., Clarke, R. and Sessions, R. An efficient, path-independent method for free-energy calculation, *J. Phys. Chem. B,* **110**, p. 17212-17220 (2006).

2048-Pos Board B67

Oxidative Footprinting of Fibrillar and Prefibrillar Oligomeric Forms of Amyloid Beta

Alexandra L. Klinger[1], Janna Kiselar[2], Mark Chance[2], Paul H. Axelsen[1].
[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Case Center for Proteomics and Bioinformatics, Cleveland, OH, USA.

Structural details of amyloid-β (Aβ) fibrils associated with plaque deposition in Alzheimer's disease (AD) remain poorly characterized. Hydroxyl radical footprinting offers a powerful method to test and develop new models of fibril topology. Herein, we present an oxidative footprinting study of fibrillar and prefibrillar Aβ40. Hydroxyl radicals for the study were produced by water hydrolysis, and specific side chain solvent accessibilities – oxidation rates – were determined by post-exposure MS/MS sequencing for fifteen residues of Aβ40 in fibrils and in oligomers. These rates are compared to the rates of the same side chains in fully solvent exposed reference peptides. Comparison reveals significant protection of key residues in both fibrillar and prefibrillar Aβ40. These data allow validation and rejection of structural models proposed previously in 2D-IR, electron microscopy, NMR, and powder diffraction studies further providing topological insight on Aβ40 quaternary assemblies.

2049-Pos Board B68

Thermodynamics of Protein Folding using a Modified Wako-Saitô-Muñoz-Eaton Model

Min-Yeh Tsai[1], Jian-Min Yuan[2], Yoshiaki Teranishi[1], Sheng Hsien Lin[1].
[1]National Chiao Tung University, Hsinchu, Taiwan, [2]Department of Physics, Drexel University, Philadelphia, PA, USA.

Relating bulk experimental measurements of protein folding to the microscopic processes that underlie the folding principle is critical in order to achieve a quantitative understanding of this complex phenomenon. One of the fundamental issues is the probe-dependence of protein folding properties. To address this issue, we had proposed a statistical model, modified from the original Wako-Saitô-Muñoz-Eaton (WSME) model [1]. The proposed model introduced site-dependent properties of proteins whose predictions can be compared with probe-dependent experiments [2]. To assess the validity of the folding properties obtained by fitting experimental data to the models, we applied both models to the case of a β-hairpin. The mean-field treatments of both models were compared with their exact solutions. By examining the folding curves, our results show that the mean-field result from our model is more satisfactory than that from the original one. Moreover, our MD simulation results also support the underlying assumptions of the modified model. Therefore, our model provides some insights into the relationship between its thermodynamic predictions and the probe-dependent experiments. Finally, I will discuss some possible applications of the proposed model, to a larger protein system with α/β motif as well as to protein aggregation.

1. Muñoz, V.; Henry, E. R.; Hofrichter, J.; Eaton, W. A., *PNAS***1998**, 95, 5872-5879
2. Tsai, M. Y.; Yuan, J. M.; Teranishi, Y.; Lin, S. H., *J. Biol. Phys.***2012**, DOI: 10.1007/s10867-012-9271-y

2050-Pos Board B69

Force-Clamp Experiments Reveal the Free Energy Profile and Diffusion Coefficient of the Collapse of Proteins

Herbert Lannon, Eric Vanden-Eijnden, Jasna Brujic.
New York University, New York, NY, USA.

We present force-clamp data on the collapse of ubiquitin polyproteins in response to a quench in the force. These nonequilibrium trajectories are analyzed using a general method based on a diffusive assumption of the end-to-end length to reconstruct a downhill free energy profile at 5pN and an energy plateau at 10pN with a slow diffusion coefficient on the order of~100nm ∧ 2/s. The shape of the free energy and its linear scaling with the protein length give validity to a physical model for the collapse. However, the length independent diffusion coefficient suggests that internal rather than viscous friction dominates and thermal noise is needed to capture the variability in the measured times to collapse.

2051-Pos Board B70

Single Molecule Force Spectroscopy Reveals Critical Roles of Hydrophobic Core Packing in Determining the Mechanical Stability of Protein GB1

Tianjia Bu[1,2].
[1]University of British Columbia, Vancouver, BC, Canada, [2]State Key Lab for Supramolecular Structure and Materials, Jilin University, Changchun, China.

Understanding molecular determinants of protein mechanical stability is important not only for elucidating how elastomeric proteins are designed and functioning in biological systems but also for designing protein building blocks with defined nanomechanical properties for constructing novel biomaterials. GB1 is a small α/β protein and exhibits significant mechanical stability. It is thought that the shear topology of GB1 plays an important role in determining its mechanical stability. Here, we combine single molecule atomic force microscopy and protein engineering techniques to investigate the effect of side chain reduction and hydrophobic core packing on the mechanical stability of GB1. We engineered seven point mutants and carried out mechanical phi-value analysis of the mechanical unfolding of GB1. We found that three mutations, which are across the surfaces of two subdomains that are to be sheared by the applied stretching force, in the hydrophobic core (F30L, Y45L, and F52L) result in significant decrease in mechanical unfolding force of GB1. The mechanical unfolding force of these mutants drop by 50−90 pN compared with wild-type GB1, which unfolds at around 180 pN at a pulling speed of 400 nm/s. These results indicate that hydrophobic core packing plays an important role in determining the mechanical stability of GB1 and suggest that optimizing hydrophobic interactions across the surfaces that are to be sheared will likely be an efficient method to enhance the mechanical stability of GB1 and GB1 homologues.

2052-Pos Board B71

A Comparative Study of Mechanical Stability of Circular Permutants during Co-Translocational Unfolding of Proteins through Mitochondrial Pore

Mahua Roy, Ioan Andricioaei.
UCI, Irvine, CA, USA.

Mitochondrial import machinery catalyses unfolding of the native precursor proteins by trapping some faster local unfolding fluctuations due to specific secondary structural element adjacent to the targeting sequence. On the rupture of the first resistant structure, the rest of the protein unfolds rapidly by cooperative unfolding during import into the mitochondrial matrix. The process of circular